

The relationship between vitamin d level and disease activity in patients with rheumatoid arthritis

Rheumatoid Arthritis

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Abstract

Aim: In this study, we aimed to reveal the relationship between disease activity level and serum 25 (OH) vitamin D level in rheumatoid arthritis (RA), a chronic autoimmune disease. **Material and Method:** Ninety-one patients with RA and 90 healthy controls were included in the study. DAS28 score and 25 (OH) vitamin D levels of the patient group and control group were compared. **Results:** The mean serum 25 (OH) vitamin D level of patients and controls were $16,8 \pm 10,1 \mu\text{g} / \text{L}$ and $28,3 \pm 16 \mu\text{g} / \text{L}$, respectively. 25 (OH) vitamin D levels were statistically significantly lower in the patients group than in the control group ($p < 0,001$). In total, serum 25 (OH) vitamin D levels and DAS28 scores of the patients were not significantly correlated ($r = -0,058$, $p = 0,588$). Correlation analysis according to sexes showed negative correlation between serum 25 (OH) vitamin D level and DAS28 score in males ($r = -0,646$, $p = 0,002$) and no correlation was found in females ($r = 0,113$, $p = 0,346$). **Discussion:** Low serum 25 (OH) vitamin D may play a role in the pathogenesis of RA patients. The significant relationship between disease activity and serum 25 (OH) vitamin D level in male gender shows that this effect is more prominent in male sex.

Keywords

DAS28; Rheumatoid Arthritis; Vitamin D

Introduction

The main source of vitamin D, which is an oil-soluble vitamin, is the cholecalciferol produced in the skin. Vitamin D, produced by sunlight (UV), is metabolized and transformed into an active form in the liver and kidneys.

Studies conducted in recent years have shown that vitamin D receptors are also involved in the immune system cells and that vitamin D may have effects on natural and acquired immunity. Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, inflammatory disease that targets synovial tissues as a primary [1,2]. Rheumatoid arthritis has the highest prevalence among the types of inflammatory arthritis seen worldwide. Although the etiology is not clearly known, it is thought that it is caused by the effects of some genetic and environmental trigger factors.

The discovery of the presence of vitamin D receptors (VDR) in various immune cells and the local vitamin D metabolism in these cells has shown that vitamin D plays an important role in the regulation of immunity [3]. 1,25-dihydroxy vitamin D acts as a kind of immunomodulator that suppresses dendritic cell maturation and functions, inhibits the proliferation of T- and B-cells, and inhibits proinflammatory excretion, thereby reducing immune system activation. For this reason, theoretically, an increase in the development of autoimmune diseases such as RA can be observed due to impaired immunological tolerance in the case of vitamin D deficiency. This has been demonstrated in animal studies [3-5].

The role of vitamin D on immunity, which is believed to be related to autoimmune diseases and that results in different outcomes in studies on this subject, is still controversial and studies are ongoing. Previously, many studies investigating the relationship between vitamin D levels and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, sjögren syndrome, ankylosing spondylitis and FMF have yielded different results [6-8]. We conducted this study to investigate the relationship between serum vitamin D levels and disease activity in patients with RA.

Material and Methods

A total of 91 patients who were referred to the Ankara Atatürk Training and Research Hospital Rheumatology polyclinic, who were diagnosed with RA according to the 2010 ACR / EULAR classification criteria and 90 healthy controls were evaluated in the study. People taking vitamin D and calcium supplements, those taking osteoporosis treatment, those with renal insufficiency, and people with inflammatory rheumatic disease other than RA were not included in the study.

Age, gender, age of onset, age at diagnosis, treatment and treatment response, smoking status, additional disease history, axial joint involvement, peripheral joint involvement, rheumatoid nodule and eye involvement were evaluated. DAS28 activity scoring was used to determine disease activity status. Deficiency of vitamin D levels was accepted as $<10 \mu\text{g/L}$, insufficiency was accepted as $10\text{-}30 \mu\text{g/L}$ and optimum level was $30\text{-}80 \mu\text{g/L}$. RF, anti-CCP, 25 (OH) vitamin D level were evaluated in patients' venous blood samples with the nephelometric method, electrochemiluminescence immunoassay (ECLIA) method, liquid chromatography-mass spectrometry (LC-MS) method respectively. In addition, complete blood count, biochemical parameters (liver and kidney function tests, electrolytes), thyroid stimulating hormone (TSH), CRP, ESH, parathyroid hormone (PTH) results were evaluated in the routine controls of the patients.

The present study was approved by Yıldırım Beyazıt University Ankara Atatürk Education Research Hospital Ethics Committee. During the study, the guidelines of the World Medical Association Helsinki Declaration and Good Clinical Practice Guidelines were followed.

Statistical Analysis

Statistical analysis of the data was performed with SPSS (Statistical Package for Social Sciences) for Windows 20.0 package program. Categorical measurements were shown as number and percentage, continuous measurements were shown as mean and standard deviation (continuous median and minimum-maximum where necessary). The Chi-Square test or Fisher's test was used to compare categorical variables.

The Student's T-test and ANOVA were used for parameters with normal distribution according to the number of variables; The Mann-Whitney U test or Kruskal-Wallis test were used for the parameters with nonnormal distribution. The Spearman and Pearson's analyzes were used for the correlation analyzes. The statistical significance level was taken as $p < 0.05$ in all tests.

Results

A total of 181 patients, 91 patients with RA and 90 control subjects without rheumatic and systemic disease were included in the study. The mean age of patients with RA was 53 ± 11 and the mean age of the control group was 50 ± 9 . The patient group consisted of 20 (22%) male, 71 (78%) female and the control group consisted of 23 male (25.6%) and 67 (74.4%) female (Table 1). There was no significant difference between the two groups in terms of age and gender ($n = 181$, $p = 0,050$, $p = 0,57$, respectively).

All patients were evaluated for RF and 53 patients (58.2%) were RF positive. Anti-CCP was evaluated in 81 patients and was positive in 47 patients (58%). When seropositive patients were evaluated together, 34 (37.3%) patients were both RF and anti-CCP positive. There was no difference between the average number of painful and swollen joints in patients with positive or negative RF and anti-CCP ($p > 0,05$).

The RA activity status of the patients was evaluated by DAS28 scoring. According to DAS28 score, 10 (11%) patients were found to have high activity, 40 (44%) had moderate activity, 17 (18.7%) had low activity, and 24 (26.4%) patients were in remission.

Deficiency of vitamin D levels was accepted as $<10 \mu\text{g/L}$, insufficiency level was accepted as $10\text{-}30 \mu\text{g/L}$ and the optimum level was $30\text{-}80 \mu\text{g/L}$. Thirty (33%) patients with RA had vitamin D deficiency, 56% (51) had insufficiency, and 11% (10) had optimal level.

In the control group, 3.3% (3) had vitamin D deficiency, 58.9% (53) had insufficiency, and 37.8% (34) had an optimum level. In patients with RA, 25 (OH) vitamin D and total protein levels were statistically significantly lower. There was no difference in the levels of calcium, phosphorus, albumin, and parathormone level between the RA patients and the control group (Table 2). Serum 25 (OH) vitamin D levels and DAS28 scores were compared in patients with RA, but no significant correlation was found between them ($r = -0.058$, $p = 0.588$). Correlation analysis according to genders revealed negative correlation between serum 25 (OH) vitamin D level and DAS28 score in males ($r = -0,646$, $p = 0,002$). There was no correlation between serum 25 (OH) vitamin D levels and DAS28 in women ($r = 0,113$, $p = 0,346$). In addition, there was no significant relationship be-

Table 1. Demographic and biochemical parameters in patient and control groups

Parameter	Groups				p sig.
	RA		Control		
	mean- Standard deviation	Median	mean- Standard deviation	Median	
Age (years)	53+/-11		50+/-9		>0.05
Disease Time (years)	6,2+/- 6,5		.		
Diagnostic Time (year)	5,7±6,6		.		
Delay in diagnosis (years)	0,5±1,2				
Painful Joint (pieces)	4+/-7		.		
Swollen Joint (pieces)	1+/-2		.		
DAS28	3,37+/-1,32		.		
Calcium (mg/dL)	9,4+/-0,4		9,2+/-0,5		>0.05
Phosphorus (mg/dL)	3,4+/-0,5		3,4+/-0,6		>0.05
Albumin (g/L)	4,4+/-0,3		4,4+/-0,3		>0.05
Total Protein (g/L)	7,0+/-0,4		7,4+/-0,4		<0.05
Vitamin D3 (ng/mL)	16,8+/-10,1	13,8	28,3+/-16	24,2	<0.05
PTH (pg/mL)	56,5+/-23,4		61,6+/-32,1		>0.05
Glucose (mg/dL)	100+/-28		.		
Urea (mg/dL)	2,59+/-2,74		.		
Creatinine (mg/dL)	0,68+/-0,16		.		
WBC (adet/mm ³)	7366+/-2415		.		
Neutrophil (adet/mm ³)	4484+/-2093		.		
Hgb (g/dL)	12,9+/-1,4		.		
Platelet (adet/mm ³)	273538+/-64206		.		
MPV (fL)	10,5+/-0,8		.		
CRP (mg/L)	10,9+/-15,5		.		

Table 2. Comparison of parameters between groups

Parameter	Grup		P
	RA	control	
	mean- Standard deviation	mean- Standard deviation	
Calcium (mg/dL)	9,4 ±0,4	9,2 ±0,5	0,076
Phosphorus (mg/dL)	3,4 ±0,5	3,4 ±0,6	0,791
Albumin (g/L)	4,4 ±0,3	4,4 ±0,3	0,879
Total Protein (g/L)	7,0 ±0,4	7,4 ±0,4	0,000
Vitamin D (ng/mL)	16,8 ±10,1	28,3 ±16	0,000
PTH (pg/mL)	56,5 ±23,4	61,6 ±32,1	0,565

tween DAS28 and 25 (OH) vitamin D groups ($p = 0,322$). When DAS28 and 25 (OH) vitamin D groups were compared in men with RA, there was a statistically significant relationship between low and moderate disease activity and insufficiency groups ($p < 0,05$). There was no significant relationship between DAS28 and 25 (OH) vitamin D groups in women ($p = 0,45$) (Table 3).

No significant difference was found between the 25 (OH) vitamin D groups and VAS values of the patients ($p = 0,65$). There was no correlation between serum 25 (OH) vitamin D levels and the disease duration of RA and the time elapsed since RA diagnosis ($r = -0,030$, $p = 0,781$, $r = -0,016$, $p = 0,879$, respectively). There was negative correlation between serum albumin level and DAS28 score ($r = -0,378$, $p = 0,000$). There was no significant correlation between serum 25 (OH) vitamin D levels and number of painful and swollen joints in patients with RA ($r = -0,065$, $p = 0,538$, $r = 0,098$, $p = 0,354$, respectively).

Discussion

In our study, vitamin D deficiency was detected in 89% of patients with RA and in 62.2% of control group. The mean value of 25 (OH) vitamin D levels of the patients were significantly lower than the control group. There was no significant correlation between DAS28 activity score and serum 25 (OH) vitamin D levels in RA patients in total. In the subgroup analysis, there was a negative correlation between DAS28 score and 25 (OH) vitamin D levels in the male patient group of RA, but no correlation was found in the female patient group. In addition, insufficiency of 25 (OH) vitamin D was found to be more frequent in the male RA patients with low and moderate disease activity in the analysis made between DAS28 scores and 25 (OH) vitamin D levels. In female sex, there was no relationship between disease activity status and serum 25 (OH) vitamin D groups.

In a study of 1191 patients and 1019 healthy control groups, Rossini et al. reported that there was no difference in serum 25 (OH) vitamin D levels between the RA patients and the control group, but there was a significant negative correlation between serum 25 (OH) vitamin D levels and DAS28 score in RA patients [09]. Similarly, when Zakeri et al. conducted a study in patients with RA, a significant negative correlation was found between disease activity determined by DAS28 score and serum 25 (OH) vitamin D levels. There was also a significant correlation between elevated VAS (visual analog scale) levels and increased number of swollen joints and low serum 25 (OH) vitamin D levels [10]. Six hundred and twenty-five RA patients (529 females, 96 males) from 13 European countries were included in a multicenter study conducted in Europe. There was a negative correlation between the 25 (OH) vitamin D levels, DAS28-CRP ($p < 0,0001$), RAID ($p = 0,04$) and HAQ ($p = 0,02$) scores in RA patients. The average serum 25 (OH) vitamin D concentration (17.62 ± 9.76 ng / ml) of the RA patients was significantly lower than the control group (18.95 ± 9.45 ng / ml) ($p = 0,01$) [11]. In a meta-analysis, 15 studies were analyzed. The serum 25(OH) vitamin D levels of 1143 RA patients were significantly lower than the control group ($p = 0,017$). The DAS28 scores and the 25 (OH) vitamin D serum levels were inversely correlated ($p = 0,000$) [12]. In our study, it was observed that there was a statistically significant inverse relationship between DAS28 disease activity score and serum 25 (OH) vitamin D levels in male population only, but no significant correlation was found between VAS, number of painful and swollen joints and serum 25 (OH) vitamin D levels.

Table 3. Comparison of DAS 28 and 25 (OH) vitamin D groups in male and female patients

25 (OH) vit D level	DAS 28 group							
	Remission		Low Activity		Moderate Activity		High Activity	
	Number And Percentage %		Number And Percentage %		Number And Percentage %		Number And Percentage %	
	Man	Woman	Man	Woman	Man	Woman	Man	Woman
deficiency	0	6	0	6	3	12	0	3
	0,0%	37,5%	0,0%	46,2%	37,5%	37,5%	0,0%	30,0%
insufficiency	5	9	4	6	5	18	0	4
	62,5%	56,2%	100,0%	46,2%	62,5%	56,2%	0,0%	40,0%
normal	3	1	0	1	0	2	0	3
	37,5%	6,2%	0,0%	7,7%	0,0%	6,2%	0,0%	30,0%

In the study performed by Turhanoğlu et al., the relationship between functional health status and disease activity and vitamin D levels were evaluated in RA patients and no difference was found. When the 25 (OH) vitamin D levels were compared according to disease activity, the serum 25 (OH) vitamin D level was found to be significantly lower in the high activity group than in the medium and low activity groups. When the low activity group was compared with the medium activity group, the 25 (OH) vitamin D levels of the medium activity group were found to be significantly lower. Serum 25-OH vitamin D levels were also found to be negatively correlated with DAS28, CRP, and HAQ [13].

In a study of 176 RA patients by Higgins et al., no significant correlation was found between vitamin D levels and DAS28 scores. However, only an inverse relationship was found between VAS and vitamin D levels. In addition, there was no significant relationship between duration of illness and serum 25 (OH) vitamin D level [14]. In a study with 35 patients in the United Arab Emirates, there was no significant correlation between serum vitamin D levels and disease activity score (DAS28) or HAQ scores [15]. In another study with patients with RA, a moderately significant negative correlation was found between serum 25 (OH) vitamin D level in active disease, pain, and number of sensitive joints and DAS28, but no significant correlation was found between parameters in the remission group [16]. In our study, we did not find a significant correlation between serum 25 (OH) vitamin D levels and DAS28 scores in patients with RA. Similar to the study of Turhanoğlu et al., but only in male gender, we found that there was a significant inverse correlation between DAS28 score and serum 25 (OH) vitamin D level.

The NHANES (The National Health and Nutrition Examination Survey) and NHANES III trials have calculated the prevalence of vitamin D deficiency and insufficiency in the American public. Serum 25 (OH) vitamin D levels of 18158 participants were examined in the NHANES III study and percentage of vitamin D insufficiency (20-30 nmol / L) was found 33% and percentage of vitamin D deficiency (<20 nmol / L) was 22%. In the NHANES study, percentage of vitamin D insufficiency was found to be 41% and the percentage of vitamin D deficiency was found to be 36% by considering the serum 25 (OH) vitamin D levels of 20289 participants [17]. In our study, deficiency of vitamin D levels was accepted as <10 µg/L and insufficiency was accepted as 10-30 µg/L. In healthy control group, these rates were 3.3% and 58.9%, respectively. In the patient group, 33% and 56% respectively. The vitamin D levels of both patient and control group were found to be lower than the American population.

The relationship between serum 25 (OH) vitamin D levels and other autoimmune/autoinflammatory diseases was also investigated. 25 (OH) vitamin D levels were significantly lower in patients with FMF and Sjögren's syndrome (SS) [6,7]. In a similar study, people with autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), polymyositis (PM), dermatomyositis (DM) and multiple sclerosis (MS) were compared with healthy adults. 25 (OH) Vitamin D levels of the patient group with RA were found to be relatively low [8]. Our study was also concluded similarly and supported the hypothesis that vitamin D deficiency may play a role in the pathogenesis and disease activity of autoimmune diseases.

In the present study, we showed that vitamin D levels were lower in patients with RA than in healthy individuals and it may be related to disease activity. Therefore, it has been shown that vitamin D levels should be routinely measured in patients with RA. Especially in men, deficiencies should be eliminated. However, the different results obtained in previous studies suggests that there is a need for prospective studies on larger patient populations.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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